REMARKS

Applicant respectfully requests reconsideration.

Claims 121-138 were previously pending in this application.

Claim 121 is amended. Support for this amendment can be found at least on page 14 lines 28-31 of the specification.

New claims 139-142 have been added. Support for the new claims can be found at least on page 14 lines 28-31 of the specification.

Claims 121-142 are pending for examination with claims 121 and 139-142 being independent claims. No new matter has been added.

Claim Objection

Claim 121 is objected to as being an improper Markush-type claim. Claim 121 has been amended to reflect proper Markush form. Reconsideration and withdrawal of this objection is respectfully requested.

Rejection under 35 U.S.C. §112

Indefiniteness

Claims 121-138 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The claims are rejected for reciting paclitaxel (generic name) and taxol (trade name). Claim 121 has been amended to delete reference to taxol. Reconsideration and withdrawal of this objection is respectfully requested.

Enablement

Claims 121-124 and 128-132 are rejected under 35 U.S.C. §112, first paragraph, as lacking enablement. According to the Examiner, the specification is "enabling for a method of treating cancer in a subject comprising administering the unmethylated immunostimulatory oligonucleotide of SEQ ID NO:246 comprising a modified backbone and a chemotherapeutic agent". However, the Examiner considers that the specification does not enable a similar method using the oligonucleotide when it lacks a phosphate backbone modification. Accordingly, the

Examiner is challenging whether an oligonucleotide comprising SEQ ID NO:246 and lacking a phosphate backbone modification is effective in the claimed method. Applicant respectfully traverses.

At the outset, Applicant wishes to clarify that the nucleotide sequence of SEQ ID NO:246 consists of four CG dinucleotides each of which contains an unmethylated C. This is clear from the sequence listing presented in Table A which contains a similar nucleotide sequence (SEQ ID NO:358) in which each of the four CG dinucleotides contains a methylated C. Accordingly, the claims embrace oligonucleotides having the nucleotide sequence of SEQ ID NO:246 which contains four CG dinucleotides each of which contains an unmethylated C.

As stated by the Examiner, an assessment of whether claims are enabled requires an analysis of the Wands factors including the nature of the invention, the breadth of the claims, the state of the art, the relative skill of those in the art, the predictability in the art, the amount of direction provided by the specification, and the presence of working examples. These factors must be taken in their totality in determining if claims are enabled. Moreover, it is the quality and not the quantity of experimentation that must be undue in order to conclude that the claims are not enabled. Applicant has already provided a Wands analysis for the pending claims and the Examiner is referred thereto. Here, Applicant focuses on these factors as they relate to oligonucleotides lacking a modified phosphate backbone.

Nature of the invention. The invention relates, inter alia, to the immunostimulatory activity of particular oligonucleotides, including oligonucleotides comprising SEQ ID NO:246. These oligonucleotides can be used for a number of therapeutic purposes including but not limited to the treatment of cancers, either alone or in combination with one or more chemotherapeutic agents. When used in combination with chemotherapeutic agents, the oligonucleotides increase the responsiveness of cancer cells to cancer therapies. The oligonucleotides may be relatively resistant to degradation. This may be achieved, for example, by modifications to the backbone and increased length. (See page 36 lines 13-21.)

Breadth of the claims. The claims relate to the use of immunostimulatory oligonucleotides comprising SEQ ID NO:246 in combination with two specific chemotherapeutic agents in the treatment of cancer. The oligonucleotides increase the

responsiveness of cancer to such chemotherapeutic agents. The oligonucleotides may comprise a modified phosphate backbone.

State of the art. At the time of filing, the art was aware of the ability to stimulate immune responses using oligonucleotides including CpG containing oligonucleotides. Such oligonucleotides comprised one or more CpG motifs as well as additional nucleotides, thereby evidencing that additional nucleotides could be joined to such motifs without loss of activity. It was also appreciated that oligonucleotides having native, unmodified backbones are immunostimulatory, and that oligonucleotides with stabilizing backbone modifications possessed longer half lives in vivo due to resistance from endogenous nucleases. (See published PCT applications WO 96/02555 and 98/18810.) The ability to make and use such oligonucleotides was also known.

Level of ordinary skill in the art. The ordinary level of skill in the art is that of a medical practitioner. The level of skill in the art inversely correlates with the amount of guidance and teaching that the Applicant must provide.

Predictability in the art. Krieg (BioDrugs 5:341-346, 1998) is cited for the teaching that oligonucleotides in which a C is replaced with a methyl-cytosine lose their immune stimulatory activity. The claimed method recites an oligonucleotide having at least four CG dinucleotides with unmethylated cytosines. The Examiner has already acknowledged that unmethylated CG dinucleotide containing oligonucleotides are enabled. Accordingly the teaching of the reference appears moot.

Agrawal et al. (Trends in Mol. Med. 8:114-121, 2002) is cited for a similar teaching and also for the teaching that GTCGTT or TTCGTT are optimal CG dinucleotides motifs for recognition by human immune cells. Applicant respectfully points out that three of the four CG dinucleotides in SEQ ID NO:246 possess one of these optimal motifs. Therefore each of the oligonucleotides used in the claimed method will possess at least three optimal CG dinucleotide motifs. Again the teaching of the reference appears moot.

Hartmann et al. (J. Immunol. 164:1617-1624, 2000) is cited for the teaching that "to have in vivo clinical utility, ODN must be administered in a form that protects them from nuclease degradation". As stated above, phosphodiester oligonucleotides having the nucleotide sequence of SEQ ID NO:246 are immunostimulatory and would be expected to work in vivo at the proper

dose. Therapeutic dose differences between oligonucleotides should not negate enablement or patentability. Therapeutic doses are routinely determined by medical practitioners. Moreover oligonucleotides can be protected from nuclease digestion apart from backbone modifications, and as a result the claims should not be limited oligonucleotides having backbone modifications.

Additionally, several post-filing references have been published on the use of CpG nucleic acids having phosphodiester backbones in the treatment of cancer in animal models. Dow et al (J. Immunol, 1999, 163, 1552-1561); Rudginsky et al (Molecular Therapy, 2001, v. 4, 347-355), Siders et al (Molecular Therapy, 2002, v. 6, p.519-527), and Lanuti et al (Cancer research, 2000, v. 60, p. 2955-2963) all describe the administration of DNA (plasmid or bacterial) having a phosphodiester backbone elicited antitumor effects in mouse models. Thus, the *in vivo* immunostimulatory effect of DNA is not limited to oligonucleotides having modified backbones.

Direction provided by the specification. The specification teaches that immunostimulatory oligonucleotides including those comprising SEQ ID NO:246 can be used to treat cancer when used alone or in combination with one or more chemotherapeutic agents, such as those recited in claim 121. The specification further teaches that such oligonucleotides are able to increase the responsiveness of cancer cells to chemotherapeutic agents. The specification teaches the common consensus sequence shared by the oligonucleotides recited in the claimed methods, the chemotherapeutic agents that can be used in combination with the oligonucleotides, and the types of cancers to be treated. The specification also teaches a number of modifications which can be made to the phosphate backbone including but not limited to phosphorothioate backbone modifications. Such modifications were known in the art at the time of filing.

Working examples. There are no working examples showing treatment of cancer using an oligonucleotide comprising SEQ ID NO:246 in combination with one or more chemotherapeutic agents. However there are examples demonstrating the immune stimulating profile of an oligonucleotide of SEQ ID NO:246 and this profile encompasses in vitro activities known to be associated with anti-cancer activity in vivo including induction of NK lytic function, B cell proliferation, and IL-6 and TNF-alpha secretion. (See at least Examples 2, 3 and 8.) In addition, Applicant submitted with the last filed response data from human clinical trials evidencing the enhancing effect of an oligonucleotide consisting of the nucleotide sequence of

SEQ ID NO:246 and having backbone modifications, when used in combination with carboplatin and paclitaxel in the treatment of non-small cell lung cancer. Applicant submits that oligonucleotides lacking backbone modifications would still be immunostimulatory in such trials and thus would be expected to function similarly. If such oligonucleotides are not protected from nuclease digestion then a higher dose or modified formulations may be required to achieve the same therapeutic effect. This does not however negate their utility in therapy. Applicant further submits that oligonucleotides possessing nucleotides in addition to those of SEQ ID NO:246 would also be expected to function similarly. Sufficient therapeutic immunostimulatory activity is imparted by the core consensus sequence of SEQ ID NO:246 and thus practicing the claimed method does not require identification of additional nucleotides or sequences.

Quantity of experimentation. The quantity of experimentation needed to make and use the invention, in view of the disclosure and the state of the art at the time of filing, is not beyond the level of experimentation routinely practiced by persons of ordinary skill in the art.

In view of the foregoing, Applicant submits that the pending claims can be practiced without undue experimentation, and thus are enabled. Reconsideration and withdrawal of this objection is respectfully requested.

Written Description

Claims 121-138 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

The Examiner considers that the claims as pending constitute new matter. Applicant respectfully traverses.

The claims recite a genus of oligonucleotides that comprise the nucleotide sequence of SEQ ID NO:246. The nucleotide sequence of SEQ ID NO:246 is highlighted in the specification as being highly immunostimulatory. (See for example page 19 lines 6-9, page 25 lines 29-31, page 31 lines 12-13 and 17, page 32 lines 4-5, page 126 line 10, page 130 lines 6-7, page 133 lines 29-31, and Figs. 4-10 and corresponding legends.) One of ordinary skill in the art would therefore appreciate the significance of this nucleotide sequence based on the specification. The genus of oligonucleotides is defined by the presence of this common consensus nucleotide sequence. The genus contains oligonucleotides consisting solely of the nucleotide sequence of

SEQ ID NO:246 as well as oligonucleotides having additional nucleotides beyond this sequence. One of ordinary skill in the art can envision additional species within the recited genus based on the teachings in the specification. As indicated by the Examiner, the specification teaches that some oligonucleotides may be 24-40 or up to 100 nucleotides in length. With respect to oligonucleotide backbone modifications, the specification teaches a variety of modifications, all of which were known in the art and none of which alters the nature of the invention.

The claims recite chemotherapeutic agents to be used with the immunostimulatory oligonucleotides. As amended claim 121 and each of new claims 139-142 is directed to a combination of SEQ ID NO:246 and a chemotherapeutic agent. Support for these chemotherapeutic agents can be found at least on pages 15 and 16. The claimed chemotherapeutics represent the standard of care for treatment of non-small-cell lung cancer. Attached is a review article describing a comparison study of chemotherapy regimens in non-small-cell lung cancer (Schiller et al, NEJM, v. 346, p. 92, 2002).

The Examiner cites case law in support of his position. Each of these cases however can be distinguished from the present claims. In In re Ruschig, the claimed compound was represented by a generic chemical structure and could only be identified based on "choices made between several variables involved". The oligonucleotides recited in the pending claims differ from the compounds of Ruschig at least because these oligonucleotides are defined by a 24 nucleotide consensus sequence that imparts immunostimulatory activity. One of ordinary skill in the art will understand that this sequence is required for immunostimulation and not any other nucleotides or sequences to be attached to is, as contrasted with Ruschig. Thus although the genus may embrace a number of species, the clear disclosure of the essential nucleotide sequence for immunostimulation in the specification distinguishes the pending claims from those of Ruschig.

A similar distinction is found with Fujikawa v. Wattanasin. In this case, the claims recited a subgenus of compounds deriving from a generic chemical structure in the specification. The claimed subgenus recited particular substituents at the various R groups, and some of these were different from the preferred substituents described in the specification. The Court found that such disclosure did not support the claimed subgenus. The instant claims and specification can be distinguished at least on the basis that the nucleotide sequence of SEQ ID NO:246 is

recited numerous times throughout the specification and is identified as being highly immunostimulatory. (See Figs. 4-10, page 31 lines 12-13, page 32 lines 4-5, page 126 lines 10-11, page 130 lines 6-7, and page 133 lines 30-31.) It is clearly distinguished from many of the other sequences recited in the specification. Moreover, it is this 24 nucleotide sequence that imparts the immunostimulatory activity of the oligonucleotides recited in the claims. This is apparently not the case with the compounds of Ruschig and Fujikawa which by contrast are important because of the particular substituents at the various R groups.

In Martin v. Mayer, the issue was whether the two terms (wires and cables) were interchangeable and the Court found that there was insufficient evidence in the specification to show that the patentee intended such meaning. The instant claims do not rely on the interchangeability of terms as support. Accordingly, the relevance of this case to the instant facts is questionable.

In In re Smith, the Court found that a specification that disclosed "at least 12 carbon atoms" did not support a claim that recited "at least 8 carbon atoms". The terms of the instant claims find explicit support in the specification, and therefore the relevance of this case to the instant facts is also questionable.

Reconsideration and withdrawal of this objection is respectfully requested.

Rejection under 35 U.S.C. §102

Claims 121-130 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Application No. 2004/0235778 A1 to Wagner et al.

Without conceding the Examiner's position or characterization of the pending claims and the cited reference, Applicant amends claim 121 to remove recitation of 5-fluorouracil. Additionally, Applicants note that Wagner et al does not specifically show injection of SEQ ID No. 80 with 5-fluorouracil for the treatment of NSCLC, as implied in the Office Action. Claim 121 and its remaining dependent claims is therefore not anticipated by Wagner et al.

Reconsideration and withdrawal of this objection is respectfully requested.

Rejection under 35 U.S.C. §103

Claims 121-138 are rejected under 35 U.S.C. §103(a) as being unpatentable over Wagner et al. in view of Maxwell et al. (Seminars in Oncology Nursing, 8(2):113-123, May 1992).

Claims 131-138 are cancelled. Claim 121 has been amended to recite the administration of carboplatin and paclitaxel, as recited in claim 131, as well as to recite that the oligonucleotide increases the responsiveness of the cancer to the chemotherapeutic agents.

A prima facie case of obviousness requires a showing of a motivation or suggestion to combine the reference teachings, a reasonable expectation of success with regards to such combination, and the combination must result in each and every limitation of the pending claims. A prima facie case of obviousness has not been made at least because the combination does not yield each and every limitation of the pending claims. The combination of references does not teach that the oligonucleotide of SEQ ID No. 246 should be administered to treat non-small cell lung cancer with the chemotherapeutic agents carboplatin and paclitaxel. The data presented appended to the prior response evidences such increased response of non-small cell lung cancer cells to carboplatin and paclitaxel when used together with an oligonucleotide having a nucleotide sequence of SEQ ID NO:246. The synergistic result achieved with this combination of agents was unexpected and not foreseen by the disclosures of Maxwell and Wagner et al. In view thereof, the pending claims are not rendered obvious by the combination of references for at least these reasons.

Reconsideration and withdrawal of this objection is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,

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